NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2003

PLAN FOR HIV-RELATED RESEARCH

II: NATURAL HISTORY AND EPIDEMIOLOGY

PREPARED BY THE OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Natural History and Epidemiology

SCIENTIFIC ISSUES

In recent years, epidemiologic research has documented marked overall declines in AIDS incidence and death in the United States and other industrialized countries, mostly attributed to a widespread use of potent antiretroviral therapy. However, the rate of decline has lately slowed down as problems have emerged such as failing therapies, inadequate access to HIV diagnosis and treatment, and incomplete adherence to complex therapeutic regimens. The HIV/AIDS epidemic in the United States continues to show increasing and disproportionate rates among minorities, women, adolescents, and injection drug users (IDUs). Recent findings among men who have sex with men have shown that new HIV infection rates might be increasing, particularly among minority men. Worldwide, studies show a global spread of a heterogeneous epidemic, which has its epicenter in Africa, but is rapidly affecting areas of high-population density in South Asia, India, and Eastern Europe. Domestically as well as internationally, the populations affected by HIV/AIDS are also those most severely affected by the spreading epidemics of sexually transmitted diseases (STDs) and tuberculosis (TB). Epidemiologic research is needed to monitor epidemic trends, develop and evaluate prevention modalities, follow the changing clinical manifestations of HIV disease in different populations, and measure the effects of treatment regimens.

PRIORITY FOR FUTURE RESEARCH:

- **Target epidemiologic studies to achieve quantitative measurements of the success and failure of prevention interventions among HIV-infected populations and their uninfected contacts. This approach includes measuring the impact of:**
  - **treatment interventions (e.g., antiviral therapy, medication adherence programs, injection drug use treatment programs) in modifying HIV spread within populations, and**
  - **treatment regimens to prevent mother-to-child HIV transmission, particularly transmission by breast-feeding.**

Treatment interventions widely used in the industrialized world since the mid-90s have been remarkably successful in improving the health and prolonging the lives of HIV-infected people and in decreasing HIV transmission from infected mothers to their offspring. Recent studies, however, have shown that these accomplishments are being threatened by the undesired side effects of such potent therapeutic regimens and the increasing emergence of HIV strains resistant to therapy. In addition, problems of access to therapy and care continue to plague minority populations in the United States. The effects of therapies on HIV transmission and on the ultimate epidemic containment is unknown. Epidemiologic research should provide the baseline information for intervention studies and proceed in parallel with intervention studies to monitor their effects on individuals and populations. Mother-to-child transmission of HIV has been studied extensively, and sizable reductions in HIV transmission rates have been achieved by simple medication regimens. Since HIV transmission that occurs through breast-feeding remains a major mode of infant infection in the developing world, a number of strategies are being investigated that are simple enough to offer hope for widespread implementation. NIH-sponsored epidemiologic studies are critical to provide the basis for tailoring interventions to widely diverse circumstances and for evaluating different strategies to prevent heterosexual and mother-to-child transmission of HIV.

PRIORITY FOR FUTURE RESEARCH:

- **Characterize how new HIV treatments lead to a changing spectrum of clinical outcomes (morbidity, adverse events, and mortality) and risk-taking behaviors.**

While the HIV/AIDS epidemic in the 1980s mainly affected white homosexual men, in the 1990s other populations such as women and drug users or their sexual partners have become a progressively larger fraction of the HIV-infected community. With dramatic progress in antiviral

therapy and its more widespread use, the clinical picture and epidemiologic features of HIV-affected populations have changed. Studies need to be conducted to confirm preliminary findings that the relationship between HIV levels and immunological status is different in women and men. In injection drug-using populations, we need to determine how injection drug use affects access to HIV treatment and adherence to it. Since recent research points to a resurgence of STDs and high-risk behaviors among men who have sex with men, to plan intervention strategies it is crucial to determine whether this resurgence of high-risk behaviors may have resulted from the availability of HIV treatments.

PRIORITY FOR FUTURE RESEARCH:

- **Develop, maintain and effectively utilize cohort studies among populations experiencing emerging epidemics (e.g., the underserved, heterosexual men and women, homosexual men with persistent risk-taking behavior, and injection drug users). Use this approach domestically and internationally to study HIV/AIDS pathogenesis and natural history in the presence of interventions, including vaccine trials.**

A prerequisite of successful interventions is the understanding of the changing pattern of HIV throughout the world and the impact of therapeutic and prevention interventions on survival and clinical outcomes. A domestic and international infrastructure must be maintained or strengthened to study biologic and behavioral aspects of HIV/AIDS in new or previously under-studied populations. NIH will continue to emphasize the importance of epidemiologic cohort studies to investigate the mechanisms of disease progression, the causes of death, and the impact of therapy in changing the spectrum of HIV disease. The strengthening of existing cohorts in the United States will allow the identification of long-term effects of HIV therapy. The assembly of new, representative cohorts, specimen repositories, and databases in developing countries will be important to study key cofactors (e.g., infectious, nutritional) that modify HIV disease.

PRIORITY FOR FUTURE RESEARCH:

- **Foster research by promoting innovative study design and analysis in observational studies and intervention trials and by developing and maintaining repositories of biological specimens.**

While observational studies, such as prospective cohort studies of HIV/AIDS can precisely define the changing relationship between therapies, outcomes, and adverse events, their methods must be constantly adjusted to

the shifting priorities of HIV research. These priorities have moved from ascertaining risk behaviors by questionnaires to assessing the prognostic value of biologic markers of disease (e.g., CD4 cell counts, viral load, genetics of the virus and the host). NIH will foster clinical, epidemiological, and biostatistical research that permits the rigorous investigation of the effects of long-term infections and of medications. Similar emphasis will be placed on methodological research in the area of randomized clinical trials, a critical instrument for establishing the merits of an ever-increasing number of therapies.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and evaluate accurate, reproducible, and affordable virologic, immunologic, and genetic assays suitable for large-scale epidemiologic research in industrialized and developing nations. Such tools should enhance our understanding of viral resistance, diversity, and evolution.**

The availability of accurate and reproducible laboratory assays has become one of the most important means to rapidly acquire knowledge of the HIV epidemic in different populations and geographic areas. Molecular biology methods are invaluable to determine key viral and host features that can be used for screening, diagnosis, and prognosis. In developing countries, simple and affordable assays are necessary to define the epidemiologic features of emerging or evolving epidemics and for clinical use in hard-to-reach locales. NIH will foster basic and applied research that will develop inexpensive virologic, immunologic, and genetic assays for use in both domestic and developing country settings.

PRIORITY FOR FUTURE RESEARCH:

- **Enhance our understanding of the interactions between HIV and concomitant infections (e.g., hepatitis C, B) and the natural history, prevention, treatment, and management of both. Investigate the implications of concomitant infections on immunogenicity and efficacy of HIV vaccine candidates.**

In industrialized countries, opportunistic infections (such as those caused by *Pneumocystis carinii*, cytomegalovirus, mycobacteria, and candida) due to HIV immune suppression have dramatically declined with the use of antiretroviral therapies. Among other infections found in HIV-infected individuals, hepatitis C virus (HCV) infection has become a much more common diagnosis, particularly among injection drug users. It is unclear to what extent and by what mechanism HIV increases HCV viral load and impairs the body immune response to HCV. The degree of additional morbidity and mortality

of HIV in people coinfected with HCV is also ill defined. Most research so far points to the presence of HCV as a particularly negative prognostic factor that results in a more rapid progression to liver disease in people with HIV infection. Assessment of the mutual impact of these two infections is important as more therapeutic options become available.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Characterize the risk factors and mechanisms of HIV transmission in domestic and international populations, to guide strategies for prevention of transmission.

STRATEGIES:

- Identify, establish, and maintain cohorts in which HIV transmission and acquisition can be assessed, including incident cohorts.
- Evaluate the impact of antiretroviral therapies on HIV transmission.
- Evaluate sexual, perinatal, and blood-borne HIV transmission and acquisition in relation to the following:
  - Viral factors, such as viral concentration in various body compartments (e.g., blood, mucosal compartments) and HIV genotype (including subtypes, recombinants, and dual virus infections).
  - Host factors, such as age, gender, hormonal status, strength and breadth of immune response, and host genetic factors.
  - Environmental factors, other infections, alcohol and other substances of abuse, other causes of oral and ano-genital inflammation, and nutrition.
  - Therapy, including adherence, duration, emergence of resistance to HIV, impact of viral load suppression on behavior, and drug effectiveness.
  - Use of microbicides and male circumcision.
  - Social, cultural, and ecologic factors, including such demographic characteristics as socioeconomic status, race, ethnicity, culture, age, and community.
  - Health care issues, including access, quality, sustainability, and education for prevention.
- Further define the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including infant feeding modalities and long-term effects of perinatal interventions.
- Quantify the effects of sexual activity, control of STDs, hygienic practices, and contraception choices on HIV transmission.

- Conduct epidemiologic studies on vaginal, rectal, penile, and oral microbicides and physical barriers to inform preventive and therapeutic interventions.
- Conduct studies on the molecular epidemiology and the effects on HIV transmission of infection with different HIV subtypes, multiple subtypes, and recombinant virus.
- Examine the prospective clinical course and markers of infectiousness among vaccine trial participants with breakthrough HIV infection to determine the vaccine's effect on population HIV incidence.
- Evaluate new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion in developing and industrialized countries.
- Evaluate risks and benefits of providing prophylaxis against HIV infection after occupational and nonoccupational exposures to HIV.
- Develop and evaluate policies promoting HIV/AIDS research among underserved and disproportionally affected populations and in areas with emerging epidemics.

OBJECTIVE:

Use epidemiologic research in domestic and international settings to identify the influence of therapeutic and other biologic (e.g., co-infections) and behavioral (e.g., access) factors on HIV progression, as shown by virologic, immunologic, and clinical outcomes.

STRATEGIES:

- Investigate differences in HIV viral load by gender to test hypothesized mechanisms of disease progression.
- Evaluate the effects of illicit drug and alcohol abuse on compliance to and effectiveness of antiretroviral therapy.
- Evaluate the impact of antiretroviral therapy on effectiveness of substance abuse treatment.
- Evaluate the impact of antiretroviral therapy on relapse to high-risk behaviors.
- Identify the spectrum of behavioral responses to initiating and continuing antiretroviral therapy.
- Characterize the changing spectrum of clinical outcomes (morbidity and mortality), including causes of death associated with evolving therapeutic strategies.
- Determine the global patterns of resistance to antiretroviral therapies and how these patterns could reduce the long-term effectiveness of antiretrovirals.
- Study factors influencing optimal clinical decision-making and patient adherence to medication regimens (modified dosage schedules, directly observed therapy [DOT]).
- Continue to characterize in adults and children the epidemiology of HIV infection and associated opportunistic infections (OIs) or conditions
- Evaluate the impact of breast-feeding on the health of HIV-infected mothers and their children, both HIV-infected and uninfected.
- Evaluate the long-term complications of antiretroviral therapy on exposed, HIV-uninfected children.

- Examine the effect of the health status of HIV-infected mothers on survival of their children, both HIV-infected and uninfected.
- Identify the effects of long-term HIV therapy on other infectious diseases; malignancies and associated oncogenic infections; cardiovascular disease; and other HIV-associated diseases, including central and peripheral nervous system conditions, cardiovascular manifestations, oral and mucosal lesions, wasting and other metabolic disorders.
- Elucidate the pathogenic mechanisms mediating HIV disease progression in well-defined population subgroups.
- Investigate the role of potential cofactors, correlates, and mediators of disease progression, including gender, immunological factors, infectious agents, hormonal factors, nutritional factors, alcohol and drug use, reexposure to HIV, and interventions such as nutritional supplementation, exercise, and other health-enhancing behaviors.
- Investigate how different patterns of adherence to drug regimens in treatment-experienced and treatment-inexperienced populations contribute to HIV drug resistance and affect disease progression.
- Study the effect on HIV disease progression of adherence to interventions in minority, adolescent, alcohol and drug-using, mentally ill, and international populations.
- Examine the impact of access to health care and of adherence to therapy regimens on health outcomes in HIV-infected populations.
- Study the effects of nutritional deficiencies, oxidative stress, and body composition on HIV disease progression.
- Develop and evaluate counseling procedures for individuals receiving HIV-related prognostic and diagnostic tests.
- Investigate the effect on disease progression of viral factors, including genotype, phenotype, and drug resistance to antiretroviral drugs.
- Study the effects of host genetic differences on disease progression and response to therapy.
- Evaluate the rate of HIV disease progression in conjunction with the effects of feasible interventions in international settings and in populations with different HIV subtypes and variable cofactors, such as nutrition and OIs.

- Assess the effect of HIV on other disease outcomes (e.g., hepatitis C, other bloodborne infections, tuberculosis, and malaria).
- Study the interaction of antiretroviral therapy, treatment for alcohol and drug use, and treatment of other infections on HIV disease progression and treatment recommendations.
- Study HIV-infected infants, children, and adolescents to determine (1) factors related to divergent rates of disease progression, (2) mechanisms that contribute to impaired growth and neurodevelopment, (3) physical and emotional impact of childhood infectious diseases and safety and efficacy of immunizations for these diseases, (4) childhood- and adolescent-specific complications, and (5) the impact of medical and behavioral treatment interventions on the items listed above.
- Study the effect of HIV infection and its treatment in aging populations with coexisting morbidities.
- Develop new cohorts and maintain long-term followup of existing cohorts, including observational cohorts and intervention populations, to determine the changing spectrum of HIV disease, especially in minority populations. Emphasis should be placed on cohorts that allow the study of possible gender effects.
- Study the emergence and re-emergence of infectious diseases and the development of antimicrobial-resistant infections, such as multidrug-resistant tuberculosis, in HIV-infected populations.
- Explore low-cost, low-technology interventions for curtailing HIV disease progression in developing countries, including nutritional interventions and better prophylaxis and treatment of OIs.

OBJECTIVE:

Develop and evaluate methods and resources for epidemiologic and clinical studies to use culturally relevant approaches; to incorporate new laboratory, sampling, and statistical methods and information systems; and to better integrate research findings into policy and practice.

STRATEGIES:

- Evaluate and incorporate the cultural context and ethical considerations in the design of studies in diverse domestic and international populations.
- Determine the most appropriate research design (e.g., observational studies versus clinical trials) to answer outstanding research questions.
- Develop and evaluate accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, and genetic assays suitable for large-scale epidemiologic research and research in developing nations. Emphasis should be on rapid HIV testing, testing for HIV superinfection, and validation of the detuned assay and noninvasive diagnostic assays for STDs, other OIs, and AIDS-related malignancies.
- Develop new biostatistical techniques to better characterize transmission dynamics, monitor and interpret disease trends, and define disease progression in different populations.
- Support a comprehensive program of interdisciplinary method research on statistical design and analysis of clinical trials with multiple interventions, community randomized HIV prevention trials, and studies of the role of social networks in HIV transmission.
- Develop innovative approaches to link records, in a manner respectful of study participant privacy, to facilitate better studies of HIV-associated diseases and mortality.
- Develop and evaluate methods to access, recruit, and retain, in biomedical preventive intervention studies, at-risk populations such as minorities, adolescents, women, substance users, incarcerated populations, and persons living with mental illness.

- Develop, maintain, and effectively utilize ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies.
- Develop and evaluate a research agenda that overcomes barriers and enhances supportive factors in the implementation of evidence-based interventions.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
AVEG/HVTN	AIDS Vaccine Evaluation Group/HIV Vaccine Trials Network
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CBO	community-based organizations
CDC	Centers for Disease Control and Prevention
CFAR	Centers for AIDS Research
CIPRA	Comprehensive International Programs in Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocytes
DC	dendritic cell
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOT	directly observed therapy
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GI	gastrointestinal

GLP/GMP	good laboratory practices/good manufacturing production
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Unviersities
HBV	hepatitis B virus
HCFA	Health Care Financing Administration
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpes virus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IHS	Indian Health Service
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpes virus
LRP	Loan Repayment Program, NIH
MAC	*Mycobacterium avium* complex
MCT	mother-to-child transmission
MDR-TB	multiple drug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organizations

NHL	non-Hodgkin's lymphoma
NHP	non-human primate
NIH	National Institutes of Health
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PHS	Public Health Service
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trials
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	Structured Treatment Interruption
TB	tuberculosis
TI	treatment interruption
UNAIDS	United Nations Joint Programme on AIDS
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study

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